Claim 62 of present application	Claim 1 of the '360 patent
A method of preventing or *inhibiting* the development of insulin dependent diabetes,	A method for preventing or *delaying* the development *of clinical symptoms* of insulin dependent diabetes
wherein said method comprises administering to a *patient,. at least 99% w/w* pure GAD protein or a fragment thereof	wherein said method comprises administering to an *animal an essentially* pure GAD protein or a fragment thereof
which, when administered to the patient, prevents or *inhibits* the development of insulin dependent diabetes	which, when administered to an animal, prevents or *delays* the development of *clinical symptoms* of insulin dependent diabetes.

As a background, insulin dependent diabetes (IDD) is an autoimmune disease that results from destruction of β-pancreatic cells that normally produce insulin. β-pancreatic cells are destroyed over a prodromal period of several years before onset of clinical symptoms of diabetes. In accordance with convention, the present application refers to patients during the prodromal period as being prediabetic, and after onset of clincial symptoms as being diabetic (see p. 1, lines 18-24). During the prodromal period, autoantibodies to a pancreatic autoantigen of 64 kDa are present in most patients (see specification, paragraph bridging pp. 1-2). The present inventors have discovered that the autoantigenic component of the 64 kDa autoantigen is a protein termed GAD. The proposed treatment of IDD with GAD is based on a mechanism whereby administration of GAD induces tolerance of the immune system to the pancreatic 64 kDa autoantigen and thereby prevents further destruction of β-pancreatic cells (see specification at p. 19, lines 16-20).

Applicants now turn to the table shown above and consider the differences in wording between the respective claims. Both of the claims have effectively three clauses, a preamble, an active method step, and a "wherein" clause that recites the effect of the active method step. The "wherein" clause of each claim is essentially the same as the preamble. The active method steps of each claim differ in wording in only two respects, shown in italics in the above claims. One claim refers to a "patient" and the other to an "animal". However, as previously noted, patients can be animals and vice versa. Accordingly, the different terminology is merely a matter of semantics.

The claims also differ in that one recites that GAD is "at least 99% w/w" pure and the other recites that GAD is "essentially" pure. Although one might debate whether "essentially pure" and "at least 99% pure" are literal equivalents in the context of a pharmaceutical, there seems little doubt that both are intended to describe GAD of sufficient purity for pharmaceutical use, and that there is no patentable distinction between them. Accordingly, no patentable distinction is seen between the active method steps of the respective claims.

The "wherein" and preamble clauses of the claims recite the consequences of performing the active method steps of the respective claims. Because there is no material difference in what is done in the respective claims, one might expect that the consequences of what is done would also be the same in the two claims, notwithstanding certain differences in wording. In applicants' view, such is the case.

The "wherein" and preamble clauses differ in wording in that one refers to "insulin dependent diabetes" and the other to "clinical symptoms of insulin dependent diabetes." In some diseases, there may be a distinction between treating a disease and treating its symptoms. For example, an antiviral agent can be used to treat the underlying disease of influenza and an aspirin to treat some of its clinical symptoms. However, according to the mechanism of action of GAD described above, administration of GAD acts only on the underlying basis of the disease (i.e., destruction of β-pancreatic cells) and does not have any effect on clinical symptoms of IDD except as a consequence of its effect on the underlying disease. Therefore, if one prevents IDD, one also prevents its clinical symptoms. Likewise, if one prevents IDD's clinical symptoms by administration of GAD, one has done so as a result of preventing the underlying disease (i.e., by preventing further β-pancreatic cell destruction). In short, in the context of administering GAD, there is no distinction, let alone patentable distinction, between preventing IDD and preventing its clinical symptoms.

Finally, the "wherein" and preamble clauses differ in that one recites "inhibiting" the other "delaying." In applicants' view, to "inhibit" development of a disease is to "delay" development of a disease or vice versa. Therefore, no distinction, let alone a patentable distinction is seen between these terms.

For these reasons, applicants submit that at least claim 62 (and claim 31 for similar reasons) is patentably indistinct from claim 1 of the '360 patent. At least certain of the dependent claims are

probably also patentably indistinct but applicants defer categorizing the dependent claims as patentably indistinct or otherwise until patentable distinctness of the independent claims has been evaluated under the appropriate legal standard discussed above.

15-23. The claims remain rejected for alleged lack of enablement. It appears that paragraph 15 of the present office action is a repeat of remarks in the previous office action (which have been addressed in the last response) and also a summary of remarks in paragraphs 16-23. Thus, applicants address the issues in turn starting with paragraph 16.

In the previous response, applicants submitted evidence of human clinical trials for use of GAD to treat diabetes. The evidence indicated that phase I human clinical trial has been successfully conducted, and a phase II trial approved. The evidence also indicated that previous articles in the scientific literature describing administration of GAD to diabetes-prone animals provided a basis for the clinical trials. The office action discounts this evidence on the basis that a successful phase I trial does not "address the concerns raised by the office action based upon the teachings by Tisch, Lernmark and Harrison that GAD administration could cause adverse effects long term, and how the treatment would be used to prevent diabetes." The office action also criticizes the evidence as "speculative" and "forward looking." In response, the office action's comments miss the point to which the evidence of clinical trials is relevant. Applicants acknowledge that a phase I trial cannot preclude the possibility of long term side effects, nor establish efficacy. Nevertheless, the fact that a phase I trial has been allowed to occur is an indication that a disinterested body of experts (i.e., the FDA or equivalent in other countries) has concluded from the relevant preclinical data including animal models, such as those in the Tisch, Lernmark and Harrison references, that the trial has a reasonable chance of success. This unsolicited and disinterested opinion of experts in the field stands in opposition to the office action's own assessment of the animal models.

The office action asks how administration of GAD can prevent or inhibit development of diabetes if the disease has already started by the time autoantibodies to GAD are detected. The answer is that clinical symptoms of diabetes do not start until the majority of β-pancreatic islet cells have been destroyed. Onset of clinical disease is preceded by a long prodromal period in which progressive destruction of β pancreatic cells occurs and autoantibodies to GAD are present (see

specification at paragraph bridging pp. 1-2 and also Tian (of record at p. 1348). If GAD is administered during the prodromal period, it will not restore any pancreatic destruction that has already occurred, but will stop or inhibit further destruction. If administration of GAD is successful in preventing further destruction, and the patient does not reach the point at which sufficient β-pancreatic cells have been destroyed then diabetes has been prevented. If administration slows but does not prevent further destruction of pancreatic cells, then the patient eventually reaches the point at which most β-pancreatic cells have been destroyed, although at a later time than if GAD had not been administered thus increasing the lag before onset of complications of the disease and consequent clinical suffering.

The office action says that applicants' own specification says that how the antigen is administered is a "key factor," and applicants have not addressed this point. If by "how the antigen is administered" the Examiner is referring to the route of administration, the present specification does not say that this is a "key factor". The specification indicates that several parenteral routes are permissible including intravenous. Further, as applicants have noted, subsequent work on animals has shown that several parenteral routes of administration can successfully be used (see Harrison, Molecular Medicine 1, 722-727 (1994)).

The Examiner is correct that the present specification does indicate that care should be taken not to potentiate an immune response. However, general principles for achieving a tolerogenic response rather than an immunogenic response were within the state of the art at the date of the invention. As was noted in the response filed October 28, 1998, a standard immunology textbook available at he priority date of the invention indicates that either low or high dosages of antigen favor a tolerogenic response, whereas intermediate dosages favor an immunogenic response (Benjamini & Leskowitz, Immunology: A Short Course (Liss, 1988) at p. 256. This textbook also indicates that absence of adjuvant and use of unaggregated antigen favor a tolerogenic response. It was also well know that an immunogenic response is unlikely to be obtained unless dosages are spaced several weeks apart (see, *Harlow & Lane, Antibodies: A Laboratory Manual* (Cold Spring Harbor Laboratory, 1988) at p. 114 providing instructions to obtain an immunogenic response in laboratory animals). Given this guidance as to the different factors favoring immunogenic and tolerogenic response, and the teaching of the specification that a tolerogenic rather than an

immunogenic response is required, it is submitted that undue experimentation would not be required to obtain a tolerogenic response.

The Examiner raises possible difficulties resulting from the existence of multiple autoantigens in diseases such as IDD. Applicants have previously pointed out that a T-cell response to GAD65 develops early in development of IDD and subsequently spreads to other β-cell antigens in a cascade of responses that ultimately lead to IDD (see Tian et al., *Nature Medicine* 12, 1348 (1996), column 1, first paragraph). Thus, it would be expected that inducing tolerance to GAD65 would abort subsequent events in the cascade of events leading to IDD. This expectation is supported by the several publications reporting that GAD65 or peptides thereof inhibit development of IDD in laboratory animals (see e.g., Tisch et al. (BO), Kaufman (BG), Tian et al., *supra*, Peterson et al., *Diabetes* 44, 1478 (1994), and Pleau et al., *J. Immunol. Immunopath.* 76, 90-95 (1995)). The Examiner acknowledges applicant's explanation but says that "each model has limitations and the models and interpretations are not limited to NOD mice." Applicants reiterate that those in the field conducting clinical trials and the regulatory authorities that have approved them do not believe that the existence of multiple antigens precludes success.

The Examiner places particular emphasis on certain remarks in the Lernmark reference stating that other investigators have not found published procedures to be easily reproducible. Applicants have previously responded that the Examiner is giving undue emphasis to a brief and passing comment at the expense of the totality of numerous publication in peer reviewed journals already of record indicating that GAD shows a pharmacological activity in treatment of IDD in animal models. In addition, it is noted that Lernmark is one of the principals of the Dyamed, the company conducting the clinical trials, so it would seem that the remark quoted from the Lernmark reference has not acted as a deterrent to Lernmark himself.

The PTO has previously cited Harrison (1995) as indicating that for the present insulin is the only antigen justifying therapeutic intervention to humans. Applicants pointed out that this 1995 reference has clearly been superseded by the clinical trials already in place. The office action discounts the clinical trials on the basis that the trials only test toxicology. Again, the office action has missed the point of why the clinical trial was cited. The fact that a regulatory body has approved a phase I trial shows that experts in the field regard administration of GAD as having a reasonable probability of success.

The PTO has previously cited a reference by Peterson discussing administration of GAD to the BB rat without apparent pharmacological effect as evidence that extrapolating from mice to humans may be misleading. Applicants have previously explained why the BB rat model may be less reliable than the NOD mouse as a predictor of efficacy in humans (response of April 14, 2000 at p. 5). The office action does not directly address applicants' position, but instead provides arguments that the NOD mouse is itself an unpredictable indicator of success in humans. The office action also argues that as applicants used rat islets in a diagnostic assay [not related to therapeutics], the rat must be an appropriate model for diabetes. Applicants reiterate for the reasons given previously that for the activity that is at issue, namely use of GAD to induce a tolerogenic response to abort further destruction of β-pancreatic cells, the NOD mouse is a more reliable indicator than the BB rat of IDD in humans. Nevertheless, whether the rat or mouse is more reliable is beside the point given that clinical trials are in progress. The fact that clinical trials are in progress indicates that those in the field conducting the trials and the regulatory body that has approved them have concluded from the totality of preclinical evidence doubtless including mice and rat that there is a reasonable probability of success.

Finally, the office action notes that the present specification does not disclose use of NOD mice or other animal. Such is not disputed. Nevertheless, the present application does disclose the strategy of administering GAD to patient as a means of inducing tolerance and thereby preventing or inhibiting destruction of β-pancreatic cells. Further, as noted in the previous response, the specification does disclose a route of administration and dosages of the same order of magnitude (taking into account differences in weight between humans and mice) as those used by others in demonstrating pharmacological activity in mice in later studies. The Examiner has also indicated that she is not criticizing the application disclosure with respect to dosages or route of administration (office action at paragraph 18).

24-25. Claims 60 and 61 stand rejected as containing new matter. These claims have been cancelled without prejudice.

26-29. Claim 31 stands rejected as anticipated by US '937. If claim 31 is viewed as being directed to the same invention as the '937 patent (as applicants submit to be the case), then the rejection can

be overcome only by interference. If claim 31 is deemed directed to a different patentable invention, then applicants can overcome the rejection by a 1.131 declaration or a declaration pursuant to MPEP 715.07(c). Applicant defer further response until the issue of same patentable invention has been addressed under the legal standard discussed above.

32-33. Claims 35, 54-57 and 62-63 stand rejected as obvious over Chang and Gottlieb. The Examiner acknowledges that Chang & Gottlieb do not teach a composition comprising GAD in a pharmaceutically acceptable carrier for human use. However, the Examiner says that it would have been obvious to modify Chang & Gottlieb's composition in view of the fact that Chang & Gottlieb teach a carrier (Freund's adjuvant) suitable for use in rats. The Examiner also reminds applicants that rats can be patients as well as humans.

In response, it is noted that claim 35 does not recite merely a "patient" but a "human patient." Although a rat might be considered to be a patient, it is not a human patient. Although it is agreed that pharmaceutically acceptable carriers for human use were known, mere knowledge of existence does not provide motivation for one to use such a carrier in place of the Freund's adjuvant used by Chang & Gottlieb. There are an infinite number of known substances that were available, and could have been combined with GAD. The issue is why one would have chosen a pharmaceutical carrier for use in humans rather than the Freund's adjuvant that Chang & Gottlieb actually used. The only reason that one would have been motivated to use such a carrier is if one intended to use GAD for administration to humans. However, the rationale for administering GAD to humans is disclosed by the present application and not by the prior art, namely, that GAD has a therapeutic activity. In the absence of motivation, the issue of "reasonable expectation of success" does not arise.

Applicants note that the office action includes method claims 62 and 63 in the above rejection, but does not supply a rationale why the cited reference applies to these claims. Because the inclusion of claims 62-63 in this rejection may have been an inadvertent error, applicants await clarification before responding.

It is noted that no art rejection is presently being applied against claims 34, 49-53, 58 or 59.

If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 650-326-2400.

Respectfully submitted,

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